REMARKS/ARGUMENTS.

Claims 3, 7, 11, 13-15, 32, and 34-36 have been withdrawn. Claim 1 is currently amended to incorporate the preferred location of the "imaging moiety" (at the Y^1 or Y^2 positions). Support can be found in the specification at page 8, lines 18-20. Since Claim 7 already has that same feature, and Claim 7 ultimately depends on claim 1, Claim 7 has been withdrawn as now redundant. In addition, the opportunity has been taken to correct the obvious errors in the dependencies of Claims 12 and 28. Applicants note that claims 34-36 are deemed withdrawn by the Examiner as being directed to a non-elected invention. Claims 1-2, 4-6, 8-10, 12, 16-31 and 33 are therefore currently pending. Clear support for the claim amendments has been cited from within the specification and/or within the withdrawn claims. Hence, Applicants respectfully submit that the amendments do not introduce new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

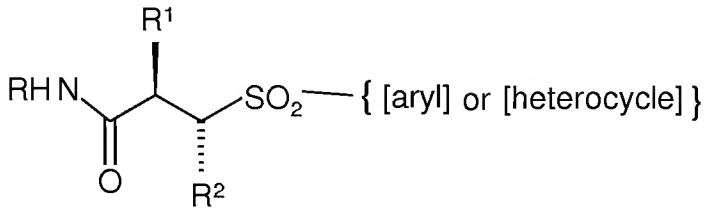
1. 35 USC §103 (Obviousness) Rejections.

All the previous claims under consideration (1-2, 4-10, 12, 16-31, and 33) continue to be rejected as being obvious over the combination of either Carpenter *et al* (WO 01/60416) or Mobashery (WO 01/92244) in view of Sahagan (EP 1088550 A1).

1.1 Carpenter and Sahagan.

Applicants stress that revised claim 1 now specifies the location of the 'imaging moiety' as an essential feature. The Examiner's unobviousness step attack is such that the teaching of Carpenter on attaching chelators etc is to be applied to the metalloproteinase inhibitors taught

by Sahagan. As noted previously, the closest chemical formula of Carpenter appears to be (Claim 8 of Carpenter), termed Formula 8A for ease of identification, where <u>X= SO_2</u>:



(A)

where: the aryl or heterocycle groups can be substituted by 0-2 R^6 groups;

R^2 is C_{1-20} alkyl;

R^6 is aryloxy substituted with 0-3 R^7;

where R^7 is Hal or methoxy.

Applicants point out that Carpenter teaches that the linking group/chelator of the MMPi of Claim 8 can be attached at specific positions:

(i) R^1 and R^4 when they together form a bridging group [p. 144 lines 4-6];

(ii) R^1 and R^2 when they together form a bridging group $-(CH_2)_3$-NH- [page 144 lines 11-13];

(iii) R^1 and R^2 when they together with the N and C atom to which they are attached form a C_{5-7} ring system [p. 144 lines 14-18];

(iv) the R^8 groups [p. 144 lines 20-23];

(vi) R^9 and $R^{9'}$ [p. 144 lines 25-32];

(vi) R^{10} and R^{11} [p. 145 lines 1-8];,

(vii) R^9 and R^{10} [p. 145lines 12-17].

The R^8, R^9, $R^{9'}$, R^{10} and R^{11} groups of Carpenter refer only to a different formula of Carpenter, and are hence irrelevant with respect to Formula 8A. The R^3 group of Carpenter is only involved when X is C=O. That means that options (ii)-(iii) above are those taught by Carpenter for the closest structural MMPis of Formula A. Those options require that the chelator is attached there only when R^1 and R^2 are combined to form either a "bridging group" $-(CH_2)_3$-NH- or form part of a C_{5-7} ring system.

Therefore, the person skilled in the art, even if assumed to be contemplating the combination of Carpenter and Sahagan, would need to assimilate the teaching of Carpenter on chelator attachment into the alleged "structurally similar" compounds of Sahagan. That would lead to cyclic structures in which one of the X^1/X^2 group of formula I of Sahagan is linked to the A group of Sahagan, and the chelator attached thereto. Such structures are outside the scope of present amended claim 1, since cyclisation or bridging of X^1/X^2 with Y^1 is outside the definitions. Present amended claim 1 requires instead that:

(a) X^1 and X^2 are cyclised together;

(b) the imaging moiety is attached at Y^1 or Y^2.

These significant differences mean that the logical combination of Carpenter/Sahagan actually teaches away from the present invention. 'Teaching away' simply means teaching a solution that would not lead to the claimed subject matter. As noted by the Federal Circuit:

A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. (emphasis added).

Para-Ordnance Mfg. v. SGS Importers Int'l, 73 F.3d 1085 (Fed. Cir. 1995).

Applicants also refer to their earlier comments as to whether the Carpenter and Sahagan references are combinable. The Examiner rejected those arguments and suggested (page 16) that C-14 is an isotope suitable for medical imaging since it is used in breath tests. Applicants acknowledge that the radioisotope ^{14}C is used in breath tests. Applicants further point out, however, that in a breath test a ^{14}C-labelled compound (eg. ^{14}C-urea) is administered to the patient. The patient's exhaled breath is subsequently analysed for $^{14}CO_2$ content, wherein the level/concentration of ^{14}C in the breath gives an indication of any metabolic abnormalities within the patient. The procedure, as the name suggests, involves a content analysis of the patient's exhaled breath (only). No image as such is involved, and certainly no image of a region of the patient's body. Applicants point out that present Claim 1 is to an "imaging agent" and hence medical imaging. That pint is made clear at the very first part of the present specification (page 1 lines 4-7). To avoid any doubt, Claim 1 has been amended to include the phrase from page 1 "suitable for diagnostic imaging *in vivo*". Therefore, a "breath test" does not constitute what the person skilled in art would understand by *in vivo* imaging, wherein a two-dimensional or three-dimensional image of a region of interest (ROI) of the patient's body (eg. an organ or area) is generated. Thus, Applicant's contend that the person skilled in art of *in vivo* medical imaging would know this, and would

hence regard ^{14}C as unsuitable for medical imaging. Applicants also point out that both ^{3}H and ^{14}C are stated in the present specification to be unsuitable imaging moieties (page 5 lines 19-20).

Applicants repeat that Sahagan, at [0043], teaches clearly that isotopically-labeled inhibitors taught therein have "...one or more atoms ..replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature." That statement completely contradicts the approach taken by Carpenter, where radiometal complexes are attached. The combination Carpenter/Sahagan is believed not to be properly combinable, because proceeding in that manner requires ignoring the clear teaching of Sahagan itself. Consequently, applicants contend that the chelator labeling methodology of Carpenter cannot be applied to Sahagan in the manner suggested by the Examiner.

Finally, Applicants reiterate their previous argument that Carpenter provides no motivation for the person skilled in the art to prepare structurally similar imaging agents. Carpenter provides 17 supporting Examples (pages 113 to 136). Carpenter discusses utility at pages 137-141. Whilst representative compounds are said to be active in *in vitro* assays (page 137, lines 28-30), there is no data which shows proof of concept for *in vivo* imaging. *In vivo* animal models of cardiovascular disease are discussed at page 140 line 9 following of Carpenter. That description is written in the present tense, i.e. is prophetic in nature. Carpenter leaves it to the person skilled in the art to test the efficacy of the vast range of imaging agents described therein. Carpenter provides no real data on any of the imaging agents claimed, so demonstration of efficacy for any of the *in vivo* imaging applications

described is absent. Applicants contend that the person skilled in the art of *in vivo* imaging would be well aware that behavior in *in vitro* assays is no guarantee or predictor of behavior in the mammalian body *in vivo*. In the absence of *in vivo* data, the person skilled in the art would not therefore be encouraged or motivated to consider building on the teaching of Carpenter by relying on its' teaching to modify Sahagan in the manner suggested by the Examiner.

In the light of the above, applicants contend that the inventive step objections based on the combination Carpenter/Sahagan should be withdrawn.

1.2 Mobashery and Sahagan.

The Examiner states (page 16), that:

> "Mobashery teaches compounds which are structurally similar (not structurally identical) to instantly claimed compounds and teaches them as matrix metalloproteinase inhibitors."

The Examiner's inventive step attack is such that the teaching of Mobashery on attaching radiolabels is to be applied to the metalloproteinase inhibitors taught by Sahagan.

Firstly, Applicants fail to see that the alleged structural similarity with Mobashery exists. Formula I (page 5 lines 1-19 & Claim 1 of Mobashery), includes the essential and distinctive feature of a 3-membered heterocyclic ring, chosen from either an epoxide (J = O), or a thiirane (J = S). Compounds 1-6 of Mobashery (Figures 1 and 2, plus Examples 1-7) all have

that feature. Mobashery in fact stresses the importance of the epoxides/thiiranes rings in the activity of the MMPis taught therein – where the O or S atom of the 3-membered ring interacts with a zinc ion (see eg. page 20 lines 3-7 plus Figures 1 and 3 of Mobashery).

Compounds 1-6 of Mobashery all also include a sulfone linkage of the type -[phenyl]-SO_2-$(CH_2)_n$-. Compounds 1-6 of Mobashery all also include an aryl ether linkage of the type [phenyl]-O-[phenyl]. All 3 of those essential features of the compounds taught by Mobashery are absent from the compounds of Formula I of present claim 1. If the broader structure (Formula I) of Mobashery is considered, then even more differences become apparent. Thus, eg. Mobashery teaches that a hydrophobic (i.e. lipophilic) group A-X-M must be present. The metalloproteinase inhibitors of formula I of present claims 1 not only lack such a group, but comprise a hydrophilic hydroxamate group instead at that position – which is the opposite characteristic. Thus, applicants fail to see that there is any real "structural similarity" with Mobashery. In fact, there are quite profound structural differences (as described above). There can therefore be no incentive for the person skilled in the art to seek to apply the teaching of Mobashery to that of Sahagan.

Applicants also refer to their above comments as to whether the Carpenter and Sahagan references are combinable. Similar logic applies to the combination of Mobashery/Sahagan. Thus, Sahagan itself at [0043] gives a clear teaching on which radiolabels are suitable, and that teaching would preclude the attachment of radiometals as chelator metal complexes. Mobashery does teach a variety of detectable radionuclides, both metallic and non-metallic. As noted above, however, Sahagan teaches clearly the need for an intrinsic (to the chemical

structure of the MMPi) radioisotope label which has uses in therapy. That would preclude most if not all of the radioisotopes taught by Mobashery. In addition, Mobashery is not really enabling for radioisotope labeling. Hence, the combination Mobashery/Sahagan is believed to lack motivation for the person skilled in the art. Applicant's position is therefore that aspect of the teaching of Mobashery is not properly combinable with Sahagan.

The Examiner argues that Mobashery provides a person skilled in the art with motivation to develop MMPis conjugated to a detectable moiety for use in diagnosis of diseases associated with MMP activity. Applicants respectfully disagree. Mobashery provides 6 supporting Examples (page 35 line 9 to page 43 line 30). All of the Examples are, however, just syntheses of the organic chemicals. Thus, Mobashery does not synthesize or test any radiolabelled compound. Example 7 of Mobashery provides *in vitro* enzyme inhibition data (Ki values) for Compounds 1-4, but those are unlabelled, non-radioactive compounds. Mobashery does not even provide a description of how the claimed radiolabelled compounds of the invention are to be prepared. Since no labeled compounds are described, and no data showing proof of concept for imaging are provided, applicants contend that the person skilled in the art could have no motivation to build other detectably labeled MMPis based on Mobashery.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejections for claims 1-2, 4-6, 8-10, 12, 16-31 and 33 under 35 U.S.C. §103(a) and direct that those claims be allowed.

6. Double Patenting.

Claims 1-2, 4-10, 13 and 16-31 are provisionally rejected under the doctrine of obvious-type double patenting, as being unpatentable over claims 1-21, 24-28, 30-31 and 35 of copending US patent application 10/544945. In response, Applicants submit that a terminal disclaimer will be filed once the instant application is indicated to be allowable.

CONCLUSION

Upon entry of this Amendment, claims 1-2, 4-6, 8-10, 12, 16-31 and 33 remain pending. Applicants submit that all outstanding issues have been addressed, and that claims 1-2, 4-6, 8-10, 12, 16-31 and 33 are in condition for allowance, which action is earnestly solicited.

The Commissioner is hereby authorized to charge any fees under 37 CFR §1.16(j) or 37 CFR 1.136(a) which may be required, or credit any overpayment, to Deposit Account No. 502-665 in the name of GE Healthcare, Inc.

Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

Respectfully submitted,

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